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OF THE CHILDREN'S HOSPITAL

WASHINGTON, D. C.

HYPEROSMOLARITY
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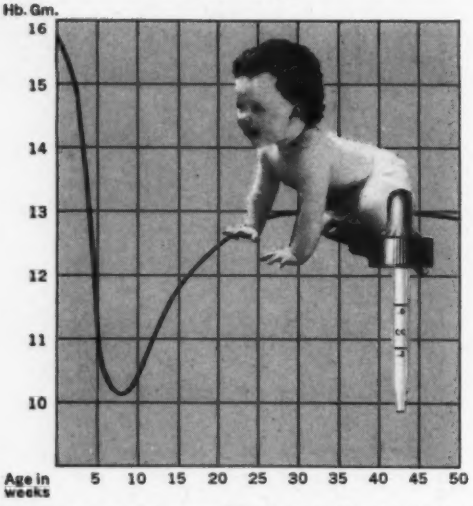

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(1) Niccum, W. L.; Jackson, R. L., and Stearns, G.: A.M.A. Am. J. Dis. Child. 86: 553, 1954. (2) Smith, C. H.: Bull. New York Acad. Med. 30: 155, 1954. (3) Smith, N. J., and Rosello, S.: J. Clin. Nutrition 1: 275, 1953. (4) Sturgeon, P.: Pediatrics 13: 107, 1954.

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HYPEROSMOLARITY

Weekly Clinical Conference

Joseph M. LoPresti, M. D.*
Sydney Ross, M. D.†
Laurence H. Kyle, M. D.‡
George E. Schreiner, M. D.§

Dr. LoPresti:

The existence of hypertonic dehydration in the face of diarrheal disease has been known for many years, having been originally described in 1911[1]. Since that time there has been a gradually increasing number of reports in the medical literature concerning this condition, variously titled hypernatremia, hyperosmolarity, or hypertonic dehydration. Many of the reports have dealt with pediatric patients; as a matter of fact, the association of gastroenteritis and hyperosmolarity has been described almost exclusively in infants under the age of one year. It is not an uncommon occurrence, having been noted in as much as twenty per cent of small infants with diarrhea. As this condition has become better publicized, the number of cases diagnosed at Children's Hospital has increased rapidly. Today we wish to describe two typical examples of this syndrome, recently diagnosed and treated at the hospital.

CASE NO. 1

This nine month old white male baby was admitted to Children's Hospital with the chief complaint of watery diarrhea of four days duration. He had been in good health until five days prior to admission, when he suddenly began vomiting. This subsided rapidly, but was followed four days prior to admission by the onset of watery diarrhea. In the four days prior to admission he had been having three to four watery green bowel movements daily and had refused most of the oral fluids offered. Two days prior to admission he was seen by his private physician, who diagnosed streptococcal pharyngitis and prescribed an injection of penicillin and paregoric. Diarrhea continued unabated, however, and the infant was admitted to the hospital for intravenous fluid therapy. Previous growth and development had been normal. Past history was non-contributory.

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Physical examination on admission revealed a markedly dehydrated infant in a state of stupor. Rectal temperature was 104°, pulse rate 170 per minute, and blood pressure 120/80. There was a marked loss of tissue turgor and a blotchy discoloration of the lower extremities. Both eardrums were reddened. The pharynx was moderately erythematous. The heart sounds were of good quality; the lungs were clear. The remainder of the physical examination was within normal limits.

The results of laboratory investigation are summarized in Table I.

Intravenous fluid therapy was initiated shortly after admission and consisted initially of 500 cc. of 5 per cent glucose in distilled water followed by 250 cc. of 5 per cent protein hydrolysate, followed by 1000 cc. of 5 per cent glucose in distilled water with added calcium gluconate (1 gram), and potassium chloride (30 mEq.). On the second day of hospitalization he received 500 cc. of 1/6 M. sodium lactate, 250 cc. of 5 per cent glucose in protein hydrolysate, and 500 cc. of 5 per cent glucose in DW. The patient gradually became rehydrated, appeared clinically improved, and was afebrile 48 hours after admission. Diarrhea continued at a reduced rate until the third hospital day, when without warning, the patient began to convulse. Following control of the convulsions by appropriate measures intravenous Ringer's solution with added potassium chloride was administered. On the fourth hospital day the patient appeared more responsive and was given a transfusion of whole blood. Recovery thereafter was rapid and complete, and he was discharged asymptomatic on the eighth hospital day.

CASE NO. 2

This ten month old white male baby was admitted to Children's Hospital with the complaint of diarrhea of three days duration. Six days prior to admission he had rhinorrhea and cough unassociated with any fever. These symptoms subsided within three days, but were followed by loose watery stools accompanied by slight fever and occasional vomiting. Diarrhea became progressively more severe, the patient having passed more than twenty watery stools on the day of admission. Growth and development were normal; past history was non-contributory.

Physical examination at the time of admission revealed an acutely ill, lethargic patient. The anterior fontanelle was depressed; his eyes were sunken. The mouth was very dry; the pharynx slightly reddened. There was moderate enlargement of the anterior cervical nodes bilaterally. The lungs contained a few scattered rhonchi. Heart sounds were of good quality. Skin turgor was very poor. The remainder of the physical examination was within normal limits.

The results of laboratory investigation are summarized in Table I.

Initial intravenous fluid therapy consisted of 150 cc. of 5 per cent glucose in 0.33 per cent normal saline. This was followed by 500 cc. of solution containing 25 mEq. Na, 20 mEq., 22 mEq. Cl, 23 mEq. lactate and 3 mEq. HPO_4 per liter with added calcium gluconate (1 gram), followed with 500 cc. of 5 per cent glucose in distilled water. Antibiotics were given intramuscularly. Oral fluids were started twelve hours after admission.

On the second hospital day, the patient appeared still somewhat dehydrated and 500 cc. of 5 per cent glucose in distilled water was administered intravenously. On the third hospital day the infant suddenly had a generalized convulsion lasting for 35 minutes before it could be brought under control. Intravenous fluid therapy was changed to the above solution. Following recovery from the convulsion, improvement was rapid and steady, and he was discharged asymptomatic on the fifth hospital day.

TABLE I

Results of Laboratory Analysis of Blood and Urine

	Hematocrit	Serum Na	Serum K	Serum Cl	Plasma carbon dioxide comb. power	Blood urea nitrogen	Urine sp. gr.	Urine reaction
	per cent	*(M.Eq./L.)*	*(M.Eq./L.)*	*(M.Eq./L.)*	*(M.Eq./L.)*	*mg./100 cc.*		
Case No. 1								
Admission.....	37	172.0	4.6	139.0	7.3		1.021	Acid
2nd Hosp. day...		145.0	3.4	120.3	5.9	75		
3rd Hosp. day...	22	143.0		97.0	19.5			
4th Hosp. day...		141.0		114.0	27.0		QNS	Acid
Case No. 2								
Admission.....				148	11.8			
2nd Hosp. day...	37	158	3.9	132	11.8		1.020	Acid
3rd Hosp. day...		140	5.6	110	14.5			

DISCUSSION

Dr. LoPresti:

I would like to concentrate primarily on the management of these patients because this is the phase in which I have been extremely interested. Our initial impression of this syndrome was that since these patients were both dehydrated and had a high serum sodium level, they had an excessive loss of water. We therefore thought that the ideal management would be to replace body water with 5 per cent glucose in distilled water, as rapidly as possible. We felt that speed was justified since it has been shown that hypernatremia and intracellular dehydration have their primary deleterious effects on the central nervous system, where actual subarachnoid hemorrhages have been described. In a series of 88 cases of hypernatremia described by Finberg[2] four previously normal infants had severe neurologic residuals. Believing this to be an acute problem, we felt the ideal management, therefore, was to give these patients large amounts of glucose in distilled water to reduce the sodium level as much as possible. This was our initial therapy in a group of some 20 patients recently diagnosed. To our amazement, as the serum sodium level returned toward normal, as renal function was established and hydration accomplished, many of these patients convulsed.

Balance studies previously carried out on patients such as these have demonstrated that two-thirds of the total water administered during treatment is added to the intracellular compartment; in other words, there is a shift of water from the extracellular to the intracellular fluid compartment. Balance studies have also shown that the absolute amount of

sodium in the extracellular fluid remains unchanged before and even during treatment so that there is no shift of sodium into or out of the extracellular space. Finberg[2] also pointed out that 28 of the 38 patients whom he examined had a low serum calcium level and he intimated that perhaps the central nervous system symptoms in these patients are on that basis. However, as far back as 1935, Kerpel-Fronious[3] stressed that hypernatremia is always accompanied by a total body deficit of sodium as well as water. *Therefore, proper therapy always requires the administration of salt as well as water in appropriate amounts.* Finberg[2] has stressed the point that optimal clinical response is obtained in infants who receive about 200 cc. per kilogram of water in the first 24 hours and sodium in amounts not to exceed 40 milliequivalents per liter.

Finberg[2] has also emphasized that administration of glucose in distilled water does not necessarily immediately cause dilution of the extracellular fluid and convulsions may occur even though the serum sodium levels are not below normal range. Weil and Wallace[4] in reporting 72 infants with hypernatremia, stressed the frequent occurrence of convulsions in the initial phase of treatment. As a matter of fact, they point out that this may be a symptom that calls attention to the syndrome. These authors have shown that *water intoxication may occur in these patients even at supernormal concentrations of serum sodium and recommend that two or three days should be taken to correct the water deficit* completely, a relatively small amount of sodium being given concurrently. Adequate rehydration can be accomplished by the administration of fluids containing a concentration of sodium of 50 to 60 milliequivalents per liter and a concentration of chlorides of 35 to 45 milliequivalents per liter. Weil and Wallace[4] recommend 180 cc. of this repair solution per kilogram of body weight per 24 hours.

Laboratory analysis of serum samples taken from our patients during or shortly after the convulsion has shown serum sodium, chloride, and carbon dioxide combining power to be within relatively normal limits. In certain patients in whom laboratory determinations of serum potassium and calcium were performed, these two cations were also found to be present in normal amounts. It is our impression, therefore, that convulsive seizures in these patients occurring on the first or second day of treatment are not due to a low calcium level. Certainly they do not behave like patients with tetany. Also, the administration of calcium in adequate amounts in these patients does not control the convulsions. However, the addition of a little salt to the intravenous fluids these patients are receiving exerts a remarkable effect. Convulsions do not recur, and the patient is soon on the way to complete recovery. Water intoxication would, therefore, appear to be the cause of the convulsion. Our present therapeutic regime for hypernatremia is to correct the hyperosmolarity slowly, over a period of two to three

days, and to include small amounts of salt in the parenteral fluids early. In the past fifteen patients managed in this fashion, no convulsions have occurred.

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Dr. Kyle:

We can do some pretty drastic things in terms of water and electrolyte replacement, and still be pretty well safeguarded because the human has two wonderful attributes: (1) He has *kidneys*. We think of these primarily as organs to get rid of waste products. But in terms of this particular problem, I think we should consider the kidneys as functioning primarily to retain the important components of the body in their proper amounts, so as to effect proper concentration of electrolytes in body fluids. In our adult patients, very frequently the kidneys are not working well, and we get into real problems. The pediatrician, of course, is more fortunate than the internist in this respect. (2) The second great defense is the sensation of *thirst*. If one loses excessive amounts of water he will drink. If he is plied with a great excess of electrolytes, he will both drink water and excrete the excess of solutes. Here the average internist is in a much better position than the pediatrician. Our patients can usually manifest the desire to drink, whereas your patients are defenseless when it comes to getting water.

To illustrate my concept of the development of this problem let us take a representative infant weighing 4 kilograms. This infant is different from the adult, fortunate in some ways, unfortunate in others. Although we are all made mostly of water, the infant has a much larger proportion than the adult. In comparing the extracellular fluid compartment, which in the adult makes up about 16 per cent of body weight, we find that in the infant it is more likely to be 30 to 40 per cent of the body weight. Even in the intracellular fluid with a proportionately large amount of solutes there seems to be more water than in the adult. Thus, body water in the child approximates 80 per cent of the lean body mass, which of course does not include fat. We must always think of the amount of water in the child or adult with reference to body fat, because the more fat the individual has, the less water. We assume, for example, that the adult has 72 per cent of water in his lean body mass. In the infant, it is undoubtedly considerably higher. In the

body mass of a person completely devoid of fat (the emaciated adult), 72 per cent of the body weight will be water, but with added fat the percentage of water decreases proportionately. A good, plump, well nourished child with a lot of fat will have proportionately much less water with which to work.

When a child begins to vomit, or has diarrhea, or loses water in any form, he obviously is not just losing water. He is also losing electrolytes. If he lost no water with these electrolytes, it is quite obvious that he would get a steady drop in serum sodium, and chloride. The child would be hyposmolar and hyponatremic, i.e., hypotonically dehydrated. In the early phase of, diarrhea, there is loss of both water and electrolytes, and electrolyte concentration is maintained. When we measure plasma and say that it contains 140 milliequivalents of sodium per liter, that does not necessarily mean that there has been no loss of sodium. It could mean that the patient has lost both water and sodium, the concentration remaining the same. So the first premise I will make, and this goes along very well with Dr. LoPresti's basic premise, is that every one of these children has lost electrolytes. After a period of time, the conservation of electrolytes is so essential that water loss then becomes the dominant problem. As the child loses water, his concentration of electrolytes begins to rise. When we see this sick child on admission to the hospital, he is then hyperosmolar, because he is concentrated, shrunken down, and he has hypernatremia, i.e., hypertonic dehydration. He is still depleted of electrolytes.

What is happening at the cellular level during this period? Obviously the initial loss of water and electrolytes involves the extracellular compartment. As soon as there is a beginning rise in osmolar concentration of sodium or any other substance that has osmolar effect, isosmotic equilibrium comes into play. The hyperosmolarity of the extracellular fluid "pulls" water from the cells, leading to cellular dehydration The major symptomatology, I suspect, in these children is due to this cellular dehydration. In addition, when the child is having diarrhea, he is obviously losing potassium, and he develops not only osmolar loss, but loss of electrolytes such as potassium that are vital to the normal function of the cell. The patient at this stage is electrolyte-depleted, in spite of the fact that he has an apparent marked increase of electrolytes in the body. Therefore, any replacement therapy in this child must involve both water and electrolytes. Up to this point, of course, I have merely elaborated on why Dr. LoPresti is completely correct. Any disagreement hereon rests with the mechanism of replacement. In view of the fact that there is marked cellular dehydration, and also loss of electrolytes, we know that the body requires two things. It needs water, and it needs electrolytes. Also, if there has been loss of potassium from the cell, such deficiency will eventually need correction.

I believe that the first thing needed for replacement is water. When we give both water and electrolytes, even as hypotonic solutions, there are two undesirable things: (1) We are giving electrolytes which at this stage of repair are not needed. (2) We are giving insufficient water. One must look at an infusion not as being 500 cc. of water, but rather in terms of available water. The higher the concentration of solutes the lesser the amount of physiologically free water available. About the only method we have of providing adequate amounts of free water, is to give water with glucose. This brings us to Dr. LoPresti's last point, which I think is vital. This child does not correct his water and electrolyte imbalance in two hours; he may may take two, three, four or five days. I suspect that Dr. LoPresti is entirely correct in saying that perhaps we can not afford to take five days to replete the child, but we certainly should not try to do it in a few hours. The first need in my mind is free water with glucose, but sometime soon that child must have replacement of his depleted electrolytes. What I suspect happened in the children described today is that the prime defect was corrected but corrected too fast. It takes time to attain equilibrium when you pour in glucose in water. We probably did not give too much water or too little electrolyte; we gave too much water too quickly. If we had given that initial water a little more slowly, we may have kept out of trouble. Or if we had given water and glucose first, and then started hypotonic electrolytes, we may have obtained a smoother recovery.

Dr. Schreiner:

Since my two predecessors have more or less confined their remarks to the problems of diarrhea, I think that it might be worth while if we step back a little bit and talk of this in general phases. What we are talking about, basically, is described by the general term dehydration, which is a rather poor term because it discusses and describes one phase of the subject under consideration. You heard Dr. LoPresti use the term, hyperosmolar or hypertonic dehydration. I would like for a moment to discuss these terms, because they have been used interchangeably in a variety of circumstances. Actually, we speak of dehydration when there is loss of body fluid from an individual. What we really mean by dehydration clinically, is loss of the extracellular fluid. This is an incorrect term, but this is what most physicians understand by the term. It is apparent that these losses can take place by a variety of routes: by routes which lost solute in excess of water; by routes or combinations of routes which lost solute in the same concentration as it exists with water and extracellular fluid; or by routes in which water is lost in excess of solute. These conditions persisting for a period of time may produce the three varieties of dehydration: (1) Hypotonic dehydration: If in the early stages one lost primarily solute, the individual

would end up dehydrated but hyposmolar; (2) Isotonic dehydration: If one tapped extracellular fluid, as used to be done in the placing of subcutaneous tubes for the treatment of nephrosis, he might remove extracellular fluid isotonically and produce isotonic contraction or dehydration; (3) Hypertonic dehydration: It also is possible in diarrheal disease to lose water in excess of solute, and end up with a hypertonic and hyperosmolar type of dehydration, as we have witnessed in these children presented today. One really can not speak in general terms of the treatment of dehydration per se. One must first categorize his patient into one of these three groups, because the approach depends specifically on which type of dehydration he is handling.

There are many causes of dehydration in children and adults besides the one we are discussing today. Perhaps the most common one in our practice is failure to drink. As Dr. Kyle mentioned, this can occur in children since they are helpless. It can also occur in old people. It can also occur in people who are stuporous, or comatose, people under the influence of drugs, alcoholics, and so forth. The common factor is the failure to ingest sufficient amount of water to maintain the solute concentration of extracellular fluid, particularly if, at the same time, the individual is eating or breaking down body cells as a source of solute. Such a person will develop hypertonic dehydration. Another cause of this type of dehydration is solute diuresis, and I think that this is perhaps one of our most common mistakes: that is, we give an individual a high metabolite or electrolyte solute load, and this can be done, remember, not just by intravenous means but also by feeding a high protein diet, as in a tube feeding. We have seen it in youngsters who are fed oral mixtures which contain many amino acids and electrolytes. It can occur just by over feeding, with an insufficient amount of water. Such an individual then presents his kidneys with a higher than normal solute load. The result is in effect an osmotic diuresis from the kidney. Here is where the physician tends to get trapped, because when he measures urine volume in an individual, and when he finds that this individual is putting out more urine than he did yesterday, he immediatelv assumes that such a patient is well hydrated because the urinary output is slowly increasing. In the case of a solute diuresis, this is quite untrue, and it is possible to dehydrate a person, by continually feeding him urea or a high protein mixture. Urine volume per se is not an index of hydration.

We can see dehydration in diabetes insipidus of the pituitary variety or of the nephrogenic variety. Just a brief look at children with nephrogenic diabetes insipidus, so-called "Water babies", will give you an indication of the real magnitude of the job of water conservation we would have if our kidneys were not in the picture. These children, of course, must spend a large part of their daily energy just drinking water. Twelve to 14 quarts

a day may be necessary to maintain water balance. We can see modifications of this in diseases which produce renal tubular damage, such as renal hyperchloremic acidosis, nephrocalcinosis with tubular damage, pyelonephritis, the recovery stage of acute renal insufficiency, the recovery stage of nephrotoxic disease, all of which present severe tubular damage. These are not like true diabetes insipidus, because they can come up to an osmotic U/P ratio of 1 or slightly over 1, but in a stress situation, they can not compensate by producing a hypertonic urine.

We have been studying the recovery stage of anuria occurring in acute renal insufficiency, and find that an inability to concentrate the urine maximally may still be present one year following a bout of acute renal insufficiency, indicating that renal tubular function is still showing improvement at the end of that time. It is quite possible that some of these individuals who have had preceding infections or exposures to nephrotoxins may actually have such a disease which keeps them from having maximum kidney compensation. The other things that we might mention briefly are the losses of hypotonic gastric juices by vomiting, or intestinal juice by diarrhea and excessive sweating. In hot weather the sweat is always hypotonic, and therefore can lead to water deficit.

What does the body do in a situation such as we are talking about today, when water is lost in excess of solute or where an abnormal solute load causes a higher concentration in the blood? The principal mechanisms are four in number. The first compensation is to extract water from the cell as previously described by Dr. Kyle. The second is to decrease the amount of sweating. When we dehydrate ourselves, there is an immediate drop in sweat volume, and in the insensible perspiration loss. This is good because it acts as a water conservation mechanism. It is bad because it provides water conservation at the expense of thermal regulation, and some individuals may develop so-called dehydration fever, which really represents failure to lose heat by evaporation of sweat. The third compensation we have is thirst, which compels us to drink more water. We have gone into the fact that infants and people who are ill may not be able to respond. The fourth compensation is to secrete anti-diuretic hormone from our posterior pituitary (if we have a normal pituitary gland), which will act on our kidneys (if we have normal kidneys). By this means, we will be able to excrete a maximumly constituted urine with the highest possible solute concentration, and therefore, conserve water over solutes.

A child with a sodium of 172 milliequivalents per liter such as occurred in the first case presented today, might be expected to be excreting the excess in the urine, such urine loss helping to take care of the situation. This, in fact, does not happen, and it is curious why it does not happen. It does not happen because dehydration of any degree does not exist without

some diminution in plasma volume. When there is a contraction of plasma volume (hemoconcentration), sodium reabsorption becomes stimulated at the renal tubules. So individuals, such as this child, although filtering more sodium through their glomeruli, are also absorbing more sodium via the tubules. This does two good things. It keeps the solutes high, so that the body is able to draw continously on intercellular water, and it also helps to keep the anti-diuretic hormone mechanism working maximumly. Perhaps it is a good compensatory mechanism, but it results in the retention of body sodium. The urinary losses of electrolyte during the genesis of this syndrome are not great. Most of the losses occur purely as a result of the antecedent diarrhea. How does this help us in treating the patient? It is my feeling that we should not treat the patient by the administration of any particular amount of water per kilogram in any particular unit of time. As we replete sodium on the basis of total body water, we should replete water in a hypertonic individual on the basis of total body water. This is where I suspect that we get into trouble. I do not think that we really know what the total body water is in these children. As Dr. Kyle brought out, this brings up the whole basic problem of body composition, and that is whether the fat child is 50 per cent water and the thin child is 70 per cent water. I think that it would be very interesting to go over the records of the type case we have had presented here today, and pick out the ones who had convulsions and see if there is any clue in their body composition. Were they the children who were plump, and therefore had a smaller body water, and therefore received a larger proportionate correction? Or were they the people who had the lower serum sodiums and received too great an amount of water for the amount of sodium retained?

If we were all sure of the percentage of normal water composition in any given child, correction of water deficit would involve only simple calculation. Let us say, for example, that a 4 kilogram infant is 60 per cent water. This infant would then have 2.4 liters of body water. In this amount of water is a concentration of serum sodium of 172 milliequivalents per liter, for example. You want approximately the same amount of body water with 140 milliequivalents. Thus $2400/X = 140/172$. X equals 2,950 cc., the amount of water necessary to give a concentration of sodium of 140 milliequivalents per liter. 2,950 cc. minus 2400 cc. equals 550 cc. water needed for replacement. This, of course, works our very nicely, but again we can not be sure if 60 per cent represents the true percentage of body water. At least it would be a more valid clinical approximation than treating all children with a set amount of water.

Another point in treating these patients is that every time you pour water back into these cells, there is going to be some potassium accompanying this water. If you will notice, both of these children had a small drop in serum potassium in the treatment phase. While it is true that you do not

want to put a lot of potassium in a child until you have established the fact that he does have a urine volume, I do not think you would go wrong if you put, say, 4 milliequivalents of potassium per liter in the glucose water used in your initial replacement. This could do no more than expand at the same concentration. This amount of potassium would not produce hyperkalemia, but it would give him that small additional amount to draw on as he is rehydrating himself.

Dr. Ross:

I would just like to mention very briefly some of the clinical features of this entity. First of all, it has been noted that the clinical manifestations of a child with excess sodium, namely hypernatremia, differ from those seen in the usual diarrhea case with normal or low sodium. I do not think that we have noted it as definitively as have Harrison, and Weil and Wallace, but they have had many more cases than we, and perhaps their observations are a lot more valid than ours. They contend that the child, (and this may be of some help clinically) does not appear so acutely dehydrated as the average diarrheal infant. His eyes are not sunken and his skin turgor is not as poor as might be expected. Perhaps more striking are the predominant central nervous system manifestations. Some of these children are stuporous, some are comatose, and some even convulse. A good many of Wallace's cases had lumbar punctures because of the fact that their clinical picture suggested meningitis. In about half of their cases, there was an increase of protein in the spinal fluid, without any increase in cells.

When infants with diarrhea are admitted to this hospital and before any laboratory work becomes available, I quite candidly confess my personal inability to distinguish clinically between hypernatremia, hyponatremia, or normal serum sodium except that these children with hypernatremia are more likely to exhibit the aforementioned central nervous system signs.

Why do these infants have central nervous system manifestations? Is it cause, or effect? I am afraid we do not know the answer. We do know that children with central nervous system lesions may have elevated serum sodiums. Does a central nervous system lesion per se, by virtue of some hypothalamic involvement (which may indeed have to do with sodium or electrolyte regulation), produce hypernatremia, or is the hypernatremia merely due to the fact that these children with brain lesions often times are lethargic and hence have a poor fluid intake? Or is it the converse, namely, does a high sodium content in the serum in ways not apparent at the present time, produce irreversible damage to the central nervous system? There is evidence in both directions, and I am afraid that all the answers are not in at the present time.

Most of the cases that we have seen at Children's Hospital have had 3,

4, and 5 days of illness, often with high fever, often with poor intake of fluids, and a fairly severe diarrhea. All these factors would be operative in producing a hypernatremia. Why the average diarrheal case does not develop hypernatremia more frequently is somewhat of a mystery to me. We have seen many infants come in with 15 or 20 stools a day for three or four days, and since the water loss would exceed the sodium loss in the stools, we wonder why we do not see more hypernatremia than we do. I do not know the answer, but it certainly is important to keep on the alert for these cases, because of the importance of proper management.

Dr. Schreiner:

I would just like to comment that in experimental animals given only seawater to drink, most of the deaths occurred as a simple cessation of respiration which was believed to be central in origin. I would think, therefore, that a serum sodium in the range of 170 to 180 represents an acute emergency. I think that you would not do any harm if you at least correct such an individual half the way back quickly, and then slow up for the rest of the way. Although we do not like to see water intoxication, as far as I know, no one has shown any real harm from mild water intoxication, in terms of permanent neurological damage.

Dr. Ross

I would like to echo Dr. Schreiner's remarks. Mortality from diarrhea at this hospital averages about 1.5 per cent. The 11.2 per cent mortality of patients with hypernatremia reported from Baltimore points up the fact that this is a condition which warrants considerable respect and is to be regarded as an acute emergency.

Question: Why have we not seen more of this syndrome in the past?

Dr. Kyle:

I suspect the increased incidence is the result of two factors: (1) Perhaps because of the increasing use of the flame photometer; increased awareness of the syndrome, and (2) the introduction of electrolyte solutions in the home. I suspect strongly that the conscientious physician who does his best to keep the child well nourished with a high protein, high electrolyte diet during a diarrheal episode, may be inducing a larger number of cases than we have seen in the past.

Dr. Ross:

I also feel that some of these cases of hypernatremia have been physician induced, either at home or in the hospital. If you give a salt solution at home, for example, unless you are careful about the amount you give, you

may get into trouble. A level teaspoon of salt which contains about 5 or 6 grams, added to a quart and a half of water, represents about a half isotonic salt solution. Some of the cases that were seen in the Baltimore clinic and in Cleveland, where two reports have emanated, were induced by the too vigorous administration of salt solution given at home.

Rapaport had a paper back in 1938 where he reported a series of cases with post-acidotic hypocalcemia, and suggested that the convulsions that were occurring in these cases were due to low calcium, but if you examine his report closely, you will find that a good many cases did not have low serum calcium. He was using high sodium chloride-containing solutions, and the incidence of convulsions during the hydration phase was considerably above the average. These might conceivably have been cases of iatrogenic hypernatremia.

PENICILLIN*

Applied Pharmacology

Sydney Ross, M.D.†

In spite of the advent of several other antibiotics within recent years, penicillin still remains the most widely used antibacterial agent in pediatrics, and in many bacterial infections it continues to be the drug of choice.

Several definite advantages account for its continuing popularity. These might be catalogued as follows: (1) low toxicity; (2) bactericidal effect; (3) advent of semisynthetic compounds such as procaine penicillin and benzathine penicillin, which have the virtue of slow absorption from the injection site; (4) less expense in comparison with other antibiotics—a 300,000-unit intramuscular dose of procaine penicillin costs less than five cents.

There are a few manifest disadvantages to penicillin, however, which make it less than the perfect antibiotic. Briefly, these would include the following: (1) limited antimicrobial spectral range—penicillin exerts little if any antibacterial activity against gram-negative bacilli; (2) resistance of strains of bacteria—this applies chiefly to the increasing number of penicillin-resistant *Staphylococcus aureus* strains; (3) resistance to peni-

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cillinase; (4) allergenicity; (5) relatively poor absorption after oral ingestion; (6) rapid excretion by the kidney; (7) poor penetration into the cerebrospinal fluid and across membranous barriers.

In spite of these shortcomings, penicillin continues to reign as the prince of antibiotics, with little likelihood that its position will be usurped in the near or distant future.

In the following discussion some of the applied pharmacologic aspects of penicillin in pediatrics will be considered, together with a summary of the present clinical indications for the drug.

SOURCE

Currently, the notatum-chrysogenum group of penicillia are the highest yielding strains and are used almost exclusively in the commercial production of penicillin. The observation that corn-steep liquor enhances the yield of penicillin manyfold has been largely contributory in accelerating production of the drug. The rich content of phenylalanine in corn-steep liquor is responsible for the latter. Production of penicillin from the mold constitutes the only method of producing large amounts of the drug, since synthetic methods have never been practical.

PHYSICAL AND CHEMICAL PROPERTIES

Chemistry

Figure 1 shows the molecular structure of all the penicillins. As will be noted, the formula is characterized by a common nucleus, and the only

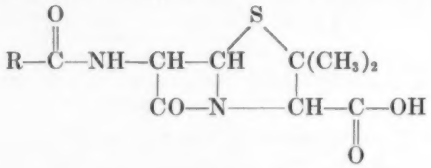

Fig. 1. Structural formula of penicillin

difference to be observed is in the nature of the side chain (R). Attention is directed to the fact that the penicillin nucleus is the chief requirement for antimicrobial activity.

Several semisynthetic penicillins have been produced, these compounds differing only in the side chain. The antibacterial activity of these semisynthetic penicillins is quite similar to that of the natural penicillins and is enumerated as follows:

Penicillin O. This semisynthetic penicillin is obtained by growing the mold in a medium containing allyl-mercaptoacetic acid. It resembles

penicillin G closely except that it may be less prone to produce allergenic reaction.

Procaine Penicillin G. Procaine penicillin G is obtained by the interaction of penicillin G and procaine. It is the most important and widely used repository penicillin preparation available today.

Benzathine Penicillin G (Bicillin or Permapen). Benzathine penicillin G is produced by a combination of one mol of N,N-dibenzylethylene diamine with 2 mols of penicillin G. This form of penicillin has considerable virtue as a long-acting repository preparation.

Penicillin V. Penicillin V, a recent addition to the semisynthetic penicillins, is obtained by replacing the benzyl radical of penicillin G with the phenoxymethyl radical. Because of the latter, penicillin V is highly insoluble in the acid medium of the stomach and passes through into the duodenum virtually unchanged. This produces higher blood levels than might be obtained with comparable doses of penicillin G.

Solubility

Both the sodium and potassium salts of penicillin are very soluble in water. On the other hand, the procaine salt of penicillin is only minimally soluble in water (0.4 per cent), while benzathine penicillin is even less soluble than procaine penicillin (0.02 per cent).

Unitage

The sodium salt of penicillin provides the standard of reference: one unit of penicillin activity equals 0.6 microgram of penicillin G. Thus 1 mg. of pure sodium penicillin G is the equivalent of 1667 units of penicillin activity.

Effect of Tissue Constituents on Penicillin

The antibacterial activity of penicillin is not impaired to any degree by tissue constituents, since there is no inhibition exerted by blood, pus or tissue autolysates. This is in marked contrast to the sulfonamides. Serum albumin forms an inactive protein complex with penicillin with 60 per cent of plasma penicillin G protein-bound. The degree of protein binding is not sufficient to neutralize the activity in vivo of penicillin G, provided the plasma levels of the drug are two to five times higher than the concentration necessary to inhibit the same organism in vitro.

ABSORPTION

Penicillin absorption is predicated on the mode of administration. The following briefly summarizes pertinent data on absorption of the drug.

Oral Administration

Penicillin G. Only about one fourth of penicillin G is absorbed from the gastrointestinal tract, since there is partial destruction by gastric acidity. After passing through the stomach, penicillin G is absorbed rapidly from the duodenum, maximum blood levels being achieved within 30 to 60 minutes after ingestion.[19, 20] Oral penicillin is preferably taken on an empty stomach about a half-hour before the next meal. Oral doses should be four to five times the intramuscular dose to produce comparable blood levels.[5]

Benzathine Penicillin. Benzathine penicillin may be administered orally with production of satisfactory blood levels. It is less influenced by concomitant food ingestion and appears to be resistant to destruction or inactivation in the gastrointestinal tract. Hence benzathine penicillin may be given without regard to meals. It is stable in aqueous suspension (unlike penicillin G) and requires no refrigeration. When a dose of 13,000 units per kilogram of body weight was administered to children, Coriell et al.[6] observed blood levels of 0.195, 0.137 and 0.083 unit per milliliter after one, two and three hours respectively. These levels were well above the maximum penicillin resistance of beta hemolytic streptococci, which is usually 0.03 unit per milliliter.

Penicillin V. This form of penicillin is stable in acid media because of the phenoxymethyl radical. Hence gastric destruction is regarded as minimal, and the drug passes through the stomach with negligible inactivation.

Intramuscular Administration

Aqueous Crystalline Penicillin. With intramuscular aqueous crystalline penicillin, peak levels are achieved within 15 to 20 minutes after injection. Hildick-Smith et al.[11] showed that optimal bactericidal levels (0.1 to 0.4 unit per milliliter) were obtained with a daily dose of 5000 units per pound given every three hours, or 10,000 units per pound every six to eight hours. Aqueous crystalline penicillin is largely reserved in current day pediatric practice for severely ill children with diseases such as meningitis, septicemia, osteomyelitis, mastoiditis, and so forth. Thus it represents primarily a hospital item and is infrequently used in office pediatric practice since the advent of the repository forms of penicillin.

Procaine Penicillin G. Procaine penicillin G has the virtue of slow absorption from the injection site. Peak plasma levels are considerably below those obtained with aqueous crystalline penicillin. Effective blood concentrations are reached within one to three hours after a single dose. Hildick-Smith et al.[11] gave procaine penicillin intramuscularly to a series

of children in doses of 6000 units per pound, producing optimal bactericidal levels for 24 hours or more after a single injection. The average blood concentration at the end of 24 hours was 0.5 unit per milliliter.

Benzathine Penicillin. Single injections of 1.2 million units of benzathine penicillin in children will result in demonstrable blood concentrations for periods up to four weeks.[22] Even though the serum concentrations of penicillin are low, they are adequate in infections caused by susceptible organisms such as beta hemolytic streptococci.

Since the advent of procaine aqueous penicillin and benzathine penicillin, other repository forms of penicillin have been largely discarded. There are definite objections in the pediatric age group to the use of other delaying agents containing sensitizing oil bases such as sesame oil, beeswax or aluminum monostearate.

TISSUE DISTRIBUTION

Eagle et al. have demonstrated the desirability of large and intermittent dosage of penicillin and the need for producing blood concentrations which are many times the minimum inhibitory concentration in vitro.[9] These investigators have also shown unequivocally the necessity for prolonged therapy in order effectively to eradicate foci of infection containing large numbers of organisms.[10] The tissue level of penicillin effective at a focus of infection is probably the same as the level effective in vitro. The bactericidal effect of penicillin in vivo against certain species of bacteria stops abruptly as soon as the plasma penicillin content falls to ineffective levels.

Intermittent intramuscular injections of aqueous crystalline penicillin are preferable to repository penicillin preparations for the eradication of deep and walled-off foci of infection.[9] The lower concentrations in the blood and tissue fluids after repository penicillin administration make it less likely that a sufficient concentration of penicillin can be brought to bear in the tissues to inhibit the causative organism. However, in instances in which the organism is sufficiently sensitive, as in beta hemolytic streptococcal infections, and when there is adequate transport of penicillin to tissue fluids, repository preparations may well suffice.

Penicillin is widely distributed throughout the body after systemic administration, but concentrations vary substantially in different tissues and body fluids. Only small amounts of penicillin enter the cerebrospinal fluid when the meninges are normal in view of the size of the penicillin molecule, which prevents ready transport across the blood-brain barrier. When the meninges are acutely inflamed, penicillin may penetrate into the cerebrospinal fluid, resulting in therapeutic concentrations. However, there is considerable variation and lack of dependability unless, as Dowling

et al. have shown, aqueous penicillin is given in massive doses in the order of one million units every two hours.[7] A dose of this magnitude will assure adequate cerebrospinal fluid concentrations.

After therapeutic doses of the drug minimal penicillin concentrations are present in brain tissue, joint spaces, and pericardial and pleural fluids, while slightly higher levels appear in peritoneal fluid. Low concentrations are present in skeletal and cardiac muscle, pancreas, spleen and adrenal gland. On the other hand, sizable concentrations appear in the blood, bile, skin, intestine and liver, and extremely high concentrations are present in the kidney.

Penicillin is rapidly excreted by the kidney, accounting for the prompt disappearance of the drug from the serum within two to four hours after a therapeutic dose of the aqueous crystalline preparation. The use of repository forms of the drug or the concomitant administration of probenecid, which blocks tubular excretion, provides for a longer duration of therapeutic serum penicillin concentrations. Renal clearance values are considerably lower in very small infants because of incomplete development of kidney function; as a result, after dosage proportionate to body surface area, the persistence of penicillin in the blood is several times as great in premature infants as in children and adults.[3]

TOXICITY AND SIDE EFFECTS

Reactions to penicillin are rare in the pediatric age group even when massive doses are given.

Local tissue irritation at the site of parenteral injections characterized by pain and induration is not infrequent, but generally is inconsequential. Occasionally peripheral nerve injury may occur, but is usually transitory. Benzanthine penicillin is considerably more irritating than procaine penicillin after intramuscular injection, especially when large doses are given.

Cutaneous skin eruptions such as urticaria, morbilliform eruptions and atopic dermatitis are the most frequent allergic manifestations of penicillin. These dermatitides may occur irrespective of the mode of administration of the drug, although hypersensitivity reactions are considerably less frequent with oral than parenteral penicillin. Penicillin sensitization may occur seven to 10 days after exposure to the drug, presenting a clinical picture closely akin to that of serum sickness; these symptoms include painful swollen joints, urticaria, fever, muscle pains and lymphadenopathy. Topical application of penicillin has resulted in a high incidence of sensitization and has been largely abandoned in favor of bacitracin, which is as effective locally as penicillin and has a low incidence of sensitization. Similarly, penicillin lozenges have no place in pediatric therapy.

Penicillin sensitization in children may occur after initial exposure or

may manifest itself at the time of subsequent administration of the drug.

The majority of allergic eruptions are controlled by discontinuation of penicillin and administration of antihistamines and/or epinephrine. The more severe reactions may be singularly benefited by the use of corticoids.

For optimum prevention of penicillin anaphylaxis, the drug should not be given for trivial conditions. Before it is administered to a child, the mother should be questioned about allergic status, previous use of penicillin and any unusual reaction to the antibiotic. Diagnostic skin and conjunctival tests to determine in advance the possibility of penicillin sensitivity are both impractical and unreliable.

Hypoallergenic penicillin preparations such as penicillin O and l-ephenamine penicillin G (Compenamine) have been developed recently. These are supposed to have a lower hypersensitivity index than penicillin G. However, there has been little critical evaluation of the virtues of these semisynthetic forms in the pediatric age group.

Parenthetically, the question frequently arises whether allergic children are more liable to sensitization to penicillin than are nonallergic children. In an attempt to answer this problem, Berkowitz et al.[4] gave penicillin to 411 children, of whom 280 were known to be allergic. Of the latter, 10 per cent had allergic reactions to the drug, whereas in the 131 nonallergic children no hypersensitivity reactions were observed. This would suggest that the administration of penicillin to allergic children carries with it a greater possibility of sensitization than in nonallergic children. However, Levin and Moss[16] in a similar controlled experiment concluded that a preexisting allergy in the child does not predispose to penicillin hypersensitivity. These investigators[16] offer an interesting possible explanation to account for the low incidence of penicillin sensitivity in children as compared with adults. They suggest that this is due in part to the relative infrequency of fungus sensitivity in younger persons and that the activity and duration of fungus infections are important in mediating such sensitivity and may account for the much greater incidence of penicillin sensitivity in adults.

It should be borne in mind that, in large doses, oral penicillin may occasionally produce gastrointestinal disturbances similar to those encountered with other antibiotics such as the tetracyclines.

DOSAGE AND ROUTES OF ADMINISTRATION

There is currently a plethora of penicillin preparations available to the physician. A confusing situation arises from the fact that a host of pharmaceutical firms attach their own names to the drug as a means of commercial identification. This multiplicity of products may indeed be likened to the

welter of vitamin preparations on the market bearing names garbled beyond all recognition. It would be wise for the pediatrician to concern himself with only a few preparations of penicillin with which he may familiarize himself and confine himself to these.

The choice of penicillin regimens depends on the nature of the infection, type of organism, and convenience and comfort to the patient. The following methods of administration are available.

Oral Penicillin

Generally speaking, for the average mild illness in the pediatric age group, oral penicillin may be used.[5, 19, 20] It has the virtue of simplicity and convenience and is less likely to produce hypersensitivity reactions than parenteral penicillin. It is advisable not to rely on oral penicillin in severe infections such as meningitis, septicemia, osteomyelitis, and so forth. Oral penicillin is useful for tapering off therapy after intramuscular penicillin has been given.

Oral penicillin may be used in the treatment of the average case of pneumococcal pneumonia and streptococcal infections in view of the marked sensitivity to penicillin of these two organisms. Similarly, oral penicillin is widely used currently in rheumatic fever prophylaxis.[14]

The three chief variants of oral penicillin include penicillin G, benzathine penicillin and penicillin V.

A recommended oral dosage schedule is indicated in Table 1.

TABLE 1

Dosage Forms of Penicillin in Pediatrics

Form of Penicillin	Maintenance Dose	Dosage Interval
Oral penicillin G	Under 30 lbs., 25,000 units/lb./24 hrs. Over 30 lbs., 600,000 units/day	Every 4–6 hrs. Give ½ hr. before meals or 2 hrs. after meals
Oral benzathine penicillin (Bicillin or Permapen)	300,000–1.2 million units/day orally	4–8 hrs.
Crystalline aqueous penicillin (sodium or potassium salt)	Under 30 lbs., 10,000 units/lb./24 hrs. IM Over 30 lbs., 300,000–600,000 units/24 hrs.	Every 3 hrs.
Procaine aqueous penicillin G	Under 30 lbs., 10,000 units/lb./24 hrs. IM Over 30 lbs., 300,000–600,000 units/24 hrs.	One injection every 24 hrs.
Benzathine penicillin IM (Bicillin or Permapen)	600,000–1.2 million units IM	Usually given as a single dose IM, or may repeat in a few days

Parenteral Penicillin

There are few children in the average pediatric practice who have not, in their short worldly sojourn, been on the receiving end of a "shot of penicillin." The ensuing struggle is generally of such intensity that the pediatrician dreads the occasion as much as the child does. However, when a child is moderately or severely ill, it is much the better part of discretion to invoke the parenteral route rather than rely on the less predictable oral administration of the drug.

The three parenteral forms in most common use today include crystalline aqueous penicillin G, procaine penicillin G and benzathine penicillin.

Crystalline Aqueous Penicillin G. Rapidly absorbed aqueous crystalline penicillin should be administered for highly resistant organisms or for organisms relatively inaccessible in body cavities or abscesses. This form of the drug can be given intramuscularly, intravenously or into body cavities. The sodium or potassium salts are most frequently used. It is stable in the dry form up to three years. Solutions buffered to pH 6 retain full potency for one week in the refrigerator. After intramuscular injection the highest penicillin serum concentration is usually achieved within one-half hour with a moderately rapid tapering off so that at the end of three hours either suboptimal levels or no demonstrable penicillin is observed in the blood. Dosage intervals range from three to six hours in the pediatric age group. The total daily dose of aqueous crystalline penicillin is given in Table 1.

Crystalline penicillin may be instilled intrathecally in a concentration not to exceed 1000 units per milliliter. Not over 5000 to 10,000 units of the drug should be administered daily intrathecally in the pediatric age group. As previously noted, there is currently little need for intrathecal penicillin in pyogenic meningitis therapy when massive doses (1,000,000 units every two to three hours) are given intramuscularly.[7]

Procaine Aqueous Penicillin G. Repository penicillins are particularly advantageous in the treatment of children in the home or office. Procaine penicillin is currently far and away the most commonly used form of the drug in pediatrics. Because of its prolonged action, only one injection a day is required. It has become common practice among pediatricians to give aqueous procaine penicillin in a dose of 300,000 units daily irrespective of the age or weight of the child. This is essentially an adult dose. However, there is only a desultory attempt on the part of physicians to base penicillin dosage on body weight in pediatrics. This is predicated on the fact that excessive amounts of penicillin are not accompanied by toxic manifestations and also that the drug is so inexpensive. This is not the case, however, with broad-spectrum antibiotics or sulfonamides. A 300,000-unit dose of procaine penicillin contains 120 mg. of procaine. This amount of procaine is rarely toxic because it is in the form of a poorly soluble salt and hence is only

slowly absorbed. Procaine penicillin should never be injected intravenously or into body cavities.

Benzathine Penicillin (Bicillin or Permapen). This long-acting repository penicillin in a dose of 1.2 million units intramuscularly produces blood levels greater than 0.05 unit per milliliter for about one month in children. This concentration, although low, would suffice in hemolytic streptococcal infections. It is generally conceded, however, that benzathine penicillin finds its greatest usefulness in prophylaxis rather than in the treatment of an acute infection. Stollerman and Rusoff[22] have reported excellent results in prophylaxis against group A streptococci in patients with rheumatic fever.

Table 1 summarizes the maintenance dose and dosage interval of penicillin in pediatrics. These dosage recommendations are at best only rough approximations, since it should be borne in mind that a knowledge of the specificity and severity of the infection, sensitivity of the organism to penicillin and an evaluation of the clinical course of the child are more important criteria for dosage than any arbitrary schedule.

GENERAL COMMENTS ON CURRENT PENICILLIN THERAPY

The Problem of Penicillin-Resistant Staphylococci

There has been a definite increase in the number of penicillin-resistant *Staphylococcus aureus* strains. Most of the data thus far reported concern hospital patients and do not necessarily reflect a similar high incidence in the general public. Resistant staphylococci are commonly found in the nares and skin of nurses and physicians in the hospital and are in all probability transmitted by cross infection from hospital attendant to patient and from one patient to another. Ludlam[17] has reported that 100 per cent of newborn infants acquired resistant staphylococci after one to 10 days in the nursery; after release of the infants from the hospital their resistant flora was lost, so that by the time they were one year old only 8.7 per cent were still carriers. Needham and Nichols[18] at Mayo Clinic reported 10 per cent carriers of resistant staphylococci in outpatients, while Dowling et al.[8] gave figures of 18 per cent carriers of penicillin-resistant strains for the public as a whole. This is in sharp contrast to the 60 to 80 per cent resistant staphylococci found in hospital populations.

Thus the problem of penicillin-resistant staphylococci is more a hospital problem than one that is indigenous to the community at large. However, it is still an acute problem which may become more serious in spite of alternative antibiotics available for therapy. The potential gravity of the situation has in part been alleviated by the discovery of new antibiotics such as erythromycin, cathomycin, vancomycin and amimycin, which may be successfully used in the treatment of resistant staphylococcal

infections. Chloramphenicol has also enjoyed considerable vogue as a useful antibiotic in such infections in view of the relative rarity (approximately 6 per cent) of chloramphenicol-resistant staphylococci.[21] On the other hand, the tetracyclines are sharing with penicillin an increasing incidence of resistant staphylococci in hospital populations. At the present writing approximately 45 to 55 per cent of staphylococci isolated from hospitalized infants and children are resistant to oxytetracycline, chlortetracycline and tetracycline.[21]

Penicillin Resistance of Organisms Other than Staphylococci

In spite of extended use of penicillin for approximately 15 years, there has fortunately been no change in the clinical efficacy of this drug against infections caused by group A beta hemolytic streptococci, pneumococci, gonococci or treponema. Sensitivities in vitro among recently isolated strains of these species show no decreasing penicillin activity. The oft-expressed fear that, as with the sulfonamides, widespread use of penicillin would result in increased resistance of many bacterial species has indeed been shown to be without basis in fact. Thus the only bona fide situation in which penicillin resistance poses any real problem remains the staphylococci. This is important to bear in mind and provides the rationale for the claim that penicillin remains the drug of choice in the majority of gram-positive coccal infections in spite of the advent of broad-spectrum antibiotics and erythromycin.

The Problem of Antagonism between Penicillin and the Broad-Spectrum Antibiotics

Much has been written regarding the antagonism between bactericidal antimicrobial agents (such as penicillin and streptomycin) and bacteriostatic drugs (such as the tetracyclines and chloramphenicol). The experimental observations of Jawetz et al. indicated that chlortetracycline, oxytetracycline and chloramphenicol are at times capable of interfering with the action of both penicillin and streptomycin.[12, 13] Lepper and Dowling[15] have added a clinical counterpart to these experimental observations in their report of 14 patients with pneumococcal meningitis treated with both penicillin and chlortetracycline, of whom 11 died, whereas in a control group treated with penicillin alone, only three cases ended fatally. However, there is little additional clinical evidence to support Jawetz's experimental observations on antagonism. Ahern and Kirby[2] treated 25 cases of pneumococcal pneumonia with a combination of chlortetracycline and penicillin and observed much the same clinical response as in a comparable control group of 25 patients treated with penicillin alone. Similarly, Walker[23] found no interference between

chloramphenicol and penicillin in the treatment of acute streptococcal pharyngitis. Ahern, Burnell and Kirby[1] found in an experimental streptococcal infection of mice that chloramphenicol inhibited the bactericidal action of penicillin only if both drugs were given in a single injection. If effective levels of the antibiotic were sustained for a period of days, no antagonism was observed. Thus clinical antagonism between penicillin and the broad-spectrum antibiotics is virtually precluded. One should have no compunction regarding the simultaneous use of penicillin and one of the broad-spectrum antibiotics in any given patient.

Weight vs. Unitage for Expressing Penicillin Dosage

It would be preferable to use weight (milligrams) rather than units to express potency of penicillin preparations even though the unit system is currently used almost exclusively. Not only is weight a more precise expression, but also it avoids misleading comparisons; e.g., one million units of penicillin sounds like a tremendous dose, whereas it is comparable to only 600 mg. of other antibiotics. An intramuscular dose of 300,000 units represents only 190 mg. of penicillin.

Effect of Massive Doses of Penicillin

High doses of penicillin are still accompanied by a low degree of toxicity, differing in this regard from other antibiotics and sulfonamides. Thus doses up to 100 million units of potassium penicillin G have been given in refractory cases of subacute bacterial endocarditis without untoward reactions.

The Indiscriminate Use of Penicillin in Pediatric Practice

One gets the impression (without any clear-cut statistical proof) that penicillin and other antibiotic agents are perhaps used more indiscriminately in children than in any other group of patients. The reason is understandable, even though one cannot necessarily condone the practice. The most common infection seen in pediatrics is the upper respiratory infection. The incidence of respiratory complications such as otitis media, cervical adenitis, bronchitis and pneumonia is inordinately high, especially in infants and young children. The pediatrician or general practitioner, seeing a child at home or in the office with an upper respiratory infection, is not likely to perform any bacteriologic laboratory studies to determine the inciting bacterial agent. Nor is a white blood cell count frequently invoked as a diagnostic aid. These studies would be routine with a hospitalized child, but the vast majority of children receiving penicillin or other antibiotics are treated outside the hospital. Thus the physician, seeing the child on a house or office visit, must make a quick decision, based entirely

TABLE 2

Therapeutic Indications for Penicillin in Pediatrics

Type of Infection	Drug of Choice	Comment
Staphylococcal:		
Acute osteomyelitis	Penicillin Erythromycin Chloramphenicol Tetracyclines	In all staphylococcal infections sensitivity of organism should be determined promptly. If organism is penicillin-sensitive, give 500,000 units aqueous crystalline penicillin every 4–6 hrs. IM for 1 week, then 600,000 units procaine aqueous penicillin IM twice daily for 3–5 weeks. Surgery necessary only in presence of large soft tissue abscesses. Danger of relapse if penicillin discontinued too soon. Recoveries approach 85%. Erythromycin or chloramphenicol alternative treatment if organism is penicillin-resistant
Chronic osteomyelitis	Penicillin Erythromycin Chloramphenicol Tetracyclines	Results not too satisfactory. Sequestrectomy necessary. Maintain penicillin therapy for 3–6 weeks. Additional local administration of penicillin (500 units/ml.) postoperatively
Furunculosis, cellulitis and soft tissue abscess	Penicillin Erythromycin Chloramphenicol Tetracyclines	Procaine aqueous penicillin 300,000 units IM initially, followed by oral penicillin for 4–7 days. Surgical drainage of pus if necessary. Erythromycin (10 mg./lb./24 hrs.) good alternative therapy.
Meningitis	Penicillin Erythromycin Chloramphenicol Tetracyclines	Prompt determination of sensitivity of organism important. Intensive therapy indicated. Give 1,000,000 units crystalline aqueous penicillin IM every 3 hrs. for 4–6 days; then continue with procaine aqueous penicillin (600,000 units twice daily) for another 7–10 days. No intrathecal penicillin necessary. If organism is penicillin-resistant, chloramphenicol and erythromycin good alternative therapy
Pneumonia	Penicillin Erythromycin Chloramphenicol Tetracyclines	Difficult to determine when causative organism of pneumonia is *Staphylococcus aureus* unless it is isolated from blood culture or empyema fluid. Give 600,000 units procaine aqueous penicillin daily IM; maintain therapy for approximately 7 days after temperature normal. When empyema is present, instill 50,000 units of penicillin daily into pleural space (1 ml. = 2000 units). If no improvement, thoracotomy necessary. Erythromycin or broad-spectrum antibiotics also effective
Cutaneous infections, including impetigo and pyoderma	Systemic: Penicillin or Erythromycin Local: Bacitracin or erythromycin ointment	Penicillin or erythromycin orally used produces rapid recovery. Topical bacitracin or erythromycin ointment efficacious in milder cases. Broad-spectrum antibiotics may also be used

TABLE 2—*Continued*

Type of Infection	Drug of Choice	Comment
Streptococcal:		
Upper respiratory infections, including pharyngitis and tonsillitis	Penicillin Tetracyclines Erythromycin Sulfadiazine	Penicillin is drug of choice in group A beta hemolytic streptococcal infections. Streptococci (group A) markedly susceptible to penicillin (0.03 unit/ml.), with penicillin-resistant strains rare. Oral penicillin yields good results. Continue penicillin therapy for 5–10 days to eradicate beta hemolytic streptococci from nasopharynx. Benzathine penicillin (1.2 million units IM as a single dose) may also be used. Rheumatic fever extremely rare when strep. throat properly treated with penicillin. Tetracyclines and erythromycin alternative therapy. Sulfadiazine less effective in eradicating beta hemolytic streptococci from oropharynx
Otitis media	Penicillin and sulfadiazine combination Broad-spectrum antibiotics	Otitis media best treated with combination of penicillin and sulfonamides. Procaine aqueous penicillin IM initially (600,000 units) followed by sulfonamides (triple sulfas) for 7 days usually adequate and precludes likelihood of relapses. Myringotomy rarely indicated
Mastoiditis	Penicillin and sulfadiazine combination Broad-spectrum antibiotics	Intensive penicillin and sulfonamide therapy required to eradicate focus and prevent relapses. Crystalline aqueous penicillin 500,000 units IM every 4 hours for 3–4 days; then switch to procaine aqueous penicillin IM (600,000 units twice daily) for one week; then taper off with oral penicillin for 2 more weeks. Concomitantly give triple sulfas (1 grain/lb./24 hrs.) for 10–14 days. Mastoidectomy rarely indicated
Scarlet fever	Penicillin Tetracyclines Erythromycin Chloramphenicol Sulfonamides	Procaine penicillin (300,000 units IM daily) or oral penicillin (800,000 units daily) for 7–10 days. Benzathine penicillin (1.2 million units IM as a single dose) also provides good therapeutic results. Any of above regimens will reduce incidence of complications and result in negative throat cultures (usually within 4–7 days). Broad-spectrum antibiotics and erythromycin also effective. Antitoxin rarely necessary
Subacute bacterial endocarditis	Penicillin Broad-spectrum antibiotics Streptomycin	Sensitivity of organism should be ascertained before therapy initiated. Approximately 600,000–900,000 units penicillin IM daily for about 1 month. Higher doses necessary if relapses occur. Periodic penicillin assays should be done. If blood culture remains positive, a combination of penicillin and streptomycin should be used. Four to 6 months' follow-up indicated

TABLE 2—*Continued*

Type of Infection	Drug of Choice	Comment
Pneumococcal:		
Pneumonia	Penicillin Broad-spectrum antibiotics Erythromycin Sulfonamides	Pneumococci very sensitive to penicillin, which remains drug of choice. Procaine aqueous penicillin 300,000 units IM daily for 4–5 days adequate in most cases. Oral penicillin 800,000 units per day also yields satisfactory results. Tetracyclines, chloramphenicol and erythromycin also effective in pneumococcal pneumonia
Meningitis	Penicillin and sulfadiazine combined Broad-spectrum antibiotics Erythromycin	Pneumococcal meningitis still a formidable disease requiring intensive therapy. Crystalline aqueous penicillin (1,000,000 units every 3 hrs. IM) and sulfadiazine (2–3 grains/lb./24 hrs.). No intrathecal therapy necessary. May substitute procaine penicillin for crystalline aqueous penicillin after 4–5 days. Continue therapy until temperature is normal and cerebrospinal fluid sterile for 10 days. Broad-spectrum antibiotics have also been used successfully. May expect 80–90 per cent recovery if infection is treated early and energetically
Gonococcal:		
Ophthalmia of the newborn	Penicillin Broad-spectrum antibiotics	Aqueous crystalline penicillin 50,000 units IM every 8 hrs. for 3 days usually adequate. Penicillin ophthalmic ointment topically is advisable. Broad-spectrum antibiotic may also be given
Vulvovaginitis, urethritis	Penicillin Broad-spectrum antibiotics	Procaine penicillin 300,000 units IM daily for 3 days curative in 95% of cases. Oral penicillin also effective in dosage of 800,000 units daily for 3 days. Criteria of cure—3 negative cultures over 21 day follow-up. If Herxheimer reaction elicitated during therapy, suspect coexistent syphilis. Broad-spectrum antibiotics also effective when treatment is continued for 4–5 days
Meningococcal:		
Meningococcemia or meningitis	Sulfadiazine Penicillin Broad-spectrum antibiotics antibiotics	Excellent results with sulfadiazine alone with 95% recovery. Give 2–3 grains/lb./24 hrs. and continue for 7 days after temperature is normal and cerebrospinal fluid sterile. Penicillin as supplementary therapy recomended. Broad-spectrum antibiotics also effective

TABLE 2—*Continued*

Type of Infection	Drug of Choice	Comment
Meningococcal:		
Fulminating meningococcemia (Waterhouse-Friderichsen syndrome)	Combination penicillin, sulfadiazine & tetracycline	Extremely vigorous therapy indicated. Aqueous crystalline penicillin 1,000,000 units every 3 hrs. IM; sodium sulfadiazine 2–3 grains/lb./24 hrs. IV and tetracycline 30 mg./lb./24 hrs. IV. In addition, adrenal cortical lipoextract 10–20 ml. every 6 hrs. IV and cortisone 100 mg. IV stat and 50–100 mg. IM/day for 3–4 days. Norepinephrine for blood pressure maintenance
	Adrenal cortical extract and cortisone	
Congenital syphilis	Penicillin	Total dose of penicillin is 200,000 units/lb. administered over a treatment period of 7–10 days. Seronegativity usually obtained within 6–12 mos. with improvement in osseous lesions within 1–3 mos. May expect 75% recovery with this regimen. Herxheimer reactions occur in moderate number of cases, but are not usually serious
Diphtheria	Antitoxin Penicillin Erythromycin	Antitoxin is prime feature of treatment. Penicillin or erythromycin useful in eradicating *C. diphtheriae* from nasopharynx
Clostridial infections (tetanus & gas gangrene	Antitoxin and Penicillin	Penicillin to be used both locally and IM, but has no antitoxic use and is to be regarded as adjunctive therapy only. Antitoxin and surgery are still mainstays of treatment

on clinical findings, whether to give an antibiotic or withhold it. A clinical estimate of whether or not a respiratory infection is due to a bacterial agent which will respond to antibiotics, or a viral agent which will not, is at best only a rough guess. Thus the temptation is strong to give antibiotics in any such equivocal situation so as "not to take any chances." This practice of giving antibiotics when in doubt is further intensified by the overt or covert pressure on the part of the parents to give the child "a shot of penicillin" or prescribe one of the new "wonder drugs." Any physician doing pediatric practice can attest to the oppressive proportions which this latter consideration can at times assume.

These are some of the factors which perhaps account for the *excessive* use of penicillin and other antibiotics in the pediatric age group. I would perhaps prefer to use the term *excessive* rather than *indiscriminate*, since the latter has a somewhat sterile connotation in view of the difficulties inherent in a situation in which only clinical indices are available to help decide whether an antibiotic is being used with or without adequate reason. In brief, one must probably accept the premise that the discriminating use

of antibiotics is frequently predicated on adequate laboratory facilities and that the latter are not generally used except in the hospitalized patient. This does not preclude intelligent use of antibiotics in the home or in the office, but admittedly makes it somewhat more difficult when only clinical criteria are available. The rapid defervescence of fever in a self-limited virus respiratory infection is frequently accepted a priori by both physician and parent alike as the direct therapeutic result of a "shot of penicillin" given the day before.

INDICATIONS

Tables 2 and 3 attempt to present a concise survey of the penicillin-susceptible infections commonly encountered in infants and children, together with a commentary on recommended dosage, duration of therapy

TABLE 3

Prophylactic Indications for Penicillin in Pediatrics

Disease	Comment
Rheumatic fever	Prophylactic therapy indicated in convalescent rheumatic fever cases. Reduction in recurrences approximately 70%. Daily dose of penicillin orally (200,000 units) usually adequate. May also use benzathine penicillin (Bicillin) in dose of 1.2 million units IM once a month. Prophylactic therapy should be administered on year-round basis until child reaches puberty
Oral surgery (i.e., T & A or tooth extraction) in children with congenital or rheumatic heart disease	Penicillin should be given for 2 days before and 3 days after oral surgery in a dose of 300,000 units procaine aqueous penicillin IM daily or 200,000 units orally 4 times a day
Meningococcus contacts	Children exposed to meningococcal meningitis should be treated with oral penicillin (200,000 units 4 times a day) for 4 days. Sulfadiazine good alternative therapy
Diphtheria contacts	If contact is Schick-negative, 300,000 units of aqueous procaine penicillin daily IM or oral penicillin (200,000 units 4 times a day) should be given for 5 days. Erythromycin (20 mg./lb./24 hrs.) excellent alternative therapy
Scarlet fever contacts	Scarlet fever contacts should receive a daily injection of 300,000 units of procaine aqueous penicillin IM or oral penicillin (200,000 units 4 times a day) for 5 days
Bacterial infections complicating viral infections such as measles, influenza, upper respiratory infections, etc.	Frequent bacterial complications in these diseases provide some justification for use of antibiotic agents such as penicillin, especially in infants or young children. Indiscriminate use of drugs should be avoided, however

and alternative modalities of therapy. It is well to emphasize, however, that recommendations regarding dosage and duration of therapy are perforce only first approximations; in the last analysis, therapy will have to be largely predicated on the severity of the illness and the response of the individual child.

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CLINICAL PATHOLOGICAL CONFERENCE

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PROTOCOL

Clinical Summary: This 10 month old white male infant was admitted to Children's Hospital because of noisy breathing and choking spells which had been present one month prior to admission.

Past History: This infant was the product of a normal gestation and normal delivery. The birth weight was 7 pound, 3 ounces. At birth it was noted that the infant had rapid respirations and at one month of age he developed a respiratory infection with breathing difficulty and mild cyanosis. At this time he was given x-ray treatment for an enlarged thymus and after two x-ray treatments he was much improved. At 2 months of age an exploratory thoracotomy was performed at which time a tumor mass in the anterior-superior mediastinum was removed. He remained asymptomatic until one month prior to admission when noisy breathing, choking spells and difficult respirations developed. X-ray examination at this time showed a mediastinal mass.

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Family History: Both parents were living and well. There were two siblings, aged 2½ and 3½ years, who had periodic symptoms of spastic colon with constipation, nausea and vomiting. There was no family history of tuberculosis, cancer or any hereditary diseases.

Physical Examination: Physical examination on admission revealed a well nourished, 10 month old white male infant; the temperature 99.4°, pulse 120, and respirations 32. Examination of the ears, nose and throat was negative. There were coarse raspy sounds on inspiration which were transmitted over the entire chest. Percussion was normal. The heart rate was regular and no murmurs were heard. There was a small umbilical hernia. No masses were palpable in the abdomen. The extremities were normal.

Laboratory Data: On admission hemoglobin 11.6 gms., RBC 3.4 million, WBC 10,000, segmented 34 per cent, bands 2 per cent, lymphocytes 60 per cent, eosinophiles 4 per cent; platelets adequate. Urinalysis on admission: clear reaction acid, specific gravity q.n.s., albumin, sugar and acetone negative. X-ray examination of the long bones and skull revealed no evidence of metastases or abnormality. The bone marrow was normal except for an increase in eosinophilic cells.

On admission the infant was placed in a steam tent and was given aureomycin 125 mg. every 8 hours. Three days after admission the infant's condition was improved and he was discharged.

DISCUSSION

Dr. Ware:

Our subject for discussion this afternoon is a 10 month old infant who is admitted because "of noisy breathing and choking spells". The respiratory history dates back to birth. Symptoms became aggravated at age one month. Apparently at that time chest films revealed an enlarged thymus and radiation therapy was given with relief. One month later symptoms were such that a thoracotomy was deemed necessary. At the time of surgery a mass "in the anterior-superior mediastinum" was removed. The patient was asymptomatic for a number of months following surgery.

Family history is not remarkable. Physical examination disclosed essentially only "raspy sounds on inspection transmitted over the entire chest". Laboratory work is not remarkable. The chest film showed a "mediastinal mass". There was no evidence of metastasis.

It would seem then that our diagnosis must be that of a mediastinal mass which can occur in infancy and is radiosensitive. The lesion tends to recur locally after removal and to cause marked symptoms due to its presence yet it did not metastasize distally.

Unfortunately no x-rays are available for study. I trust that the person

who prepared the protocol was accurate in his description of the mass in the anterior-superior mediastinum. My whole case rests on this location.

The most common mediastinal tumors are: Neurogenic tumors, pericardial cysts, bronchogenic cysts, duplications of the alimentary tract, dermoid cysts, lymphoma, thyroid tumors and thymic tumors.

Neurogenic tumors: a) Peripheral nerves, neurilemma (Schwann cells), ganglioneuroma (ganglion cells). b) Sympathetic ganglion, mature ganglioneuroma, immature or undifferentiated cells, neuroblastoma. c) Paraganglionic cells, pheochromocytoma and paraganglioma. All of these tumors may occur in the thorax. We have recently had experience with the first instance of thoracic neuroblastoma seen in this hospital. I do not believe this tumor under discussion to be of neurogenic origin. Such neurogenic tumors are classically posterior mediastinal in position. Indeed Tebow and Brown reviewed 217 mediastinal tumors of neurogenic origin and only 9 were in the anterior or mid-mediastinum.

Pericardial Coelomic Cysts: This entity is a unilocular structure which is intimately attached to the pericardium. The lesion is due to persistence of the embryonic ventral parietal recesses; hence it is located in the anterior cardiophrenic angle. The dorsal parietal recesses are known to us as the pleuro-peritoneal canals.

Pericardial Cyst: Pericardial cyst is not the entity which we seek, for the symptoms seen are not so dramatic as those described in the protocol. It does not respond to x-ray, does not recur after excision and is located in the anterior inferior mediastinum.

Bronchiogenic Cyst: (First reported by Meyer in 1859). The lungs embryologically arise from the foregut as the "tracheal bud". If a portion of this bud or anlage, becomes separated it will develop as a cystic structure containing the elements of the trachea and bronchus. Such elements include fibrous tissue, smooth muscle, cartilage and a lining of flattened or columnar ciliated epithelium.

Such cysts may have a connection with the tracheo-bronchial tree. Symptoms occur if the cyst is large enough to press on the trachea or if it becomes infected. Malignancy is extremely rare although fibrosarcoma has been reported.

These cysts do not concern us today since they are posterior mediastinal in position (near bifurcation of trachea), should not recur after excision and are not radiosensitive.

Thoracic Duplications of the Alimentary Tract: (Gastrogenic cysts, enteric cyst, foregut cyst). These tumors were first described by Blasius in 1711. They are tubular structures attached to the alimentary tract and possessing a mucous membrane. Approximately 80 such cases have been reported.

The usual attachment is of course to the esophagus in the posterior

mediastinum. They usually cause respiratory symptoms: dyspnea, cough, cyanosis. If the mucous membrane is gastric in type, peptic ulcerations may occur. This group would not seem to correspond with the protocol's description.

Dermoid Cysts and Teratomata of the Mediastinum: The first such tumor of the mediastinum was reported by Gordon in 1923. Two staff members of this hospital, Drs. Kerr and Warfield, published in 1928 one of the classical papers on this condition.

These tumors may be asymptomatic, or cause pressure symptoms (cough, dyspnea, pain) or symptoms associated with suppuration if infection supervenes.

One usually describes the dermoid variety as cystic and benign, the teratomas as frequently malignant and metastasizing widely. Both varieties occur in the anterior mediastinum. Such an entity could well fit the picture described in the protocol.

Lymphoma: By this term I include all the malignant lymphoma groups. The mediastinal nodes may be affected primarily in connection with other lymphatic chains. Lymphosarcoma is most common in males, the age range of 30 to 40 years are most affected.

When mediastinal involvement is primary, usually the nodes are in the anterior mediastinum; fever, anemia and systemic symptoms are the rule.

Malignant lymphoma would not remain local but would manifest widespread involvement with recurrence, and the patient would not improve on treatment given.

Thyroid Tumors: Thyroid tumors may involve the superior mediastinum either as a downward projection of a cervically enlarged thyroid or as an "aberrant thyroid". To explain the latter term one must remember that one anlage of the thyroid is from the pharyngeal pouch which is at the level of the embryonic pericardium; hence a thoracic thyroid is possible.

There is no mention of a cervical mass; there is no mention of radioactive iodine uptake. In addition the age of patient, recurrence of tumor and response to radiation, all would seem to rule out thyroid.

Thymic Tumor: The thymus is a ductless gland located in the superior mediastinum. The precise function is unknown. The gland is relatively large at birth and slowly regresses during childhood. Its size in infancy has led to the belief that the gland causes respiratory difficulty due to mechanical pressure on trachea or vagal nerves. This theory was first proposed by Kopp in 1824. The theory was revived when chest radiography became common.

Proponents of this theory have advised radiation therapy to thymus to shrink the gland and relieve symptoms. If such treatment is advised it should be done with caution. Several reports have recently appeared

pointing out that some children and adolescents with carcinoma of thyroid had previously received irradiation to the thymus.

The objection which I have to the theory is the realization that chest films in infants are subject to many variables. Position of the child, phase of respiratory or cardiac cycle, all greatly vary the x-ray picture. The mediastinum may look differently in x-rays of the same child done 10 minutes apart.

Although I am in discord with thymic hyperplasia as a cause of symptoms, I am impressed with the possibility of thymic neoplasm. Such tumors have characteristics which fit the case at hand. Pathologically it is difficult to distinguish benign from malignant tumors. Distant metastases are rare, the malignant tumor is noted for local infiltration and invasion. Such properties make complete removal difficult and recurrence common.

Thymic tumors are not common. The Cleveland Clinic has reported 26 cases, the youngest patient 28 years of age. The Mayo Clinic has reported 45 cases with the youngest patient listed as 16 years of age. Gross has had experience with three patients, the ages are noted as five, seven and fourteen years of age.

Despite the age of the patient in the protocol, I believe that the diagnosis is malignant thymoma.

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PATHOLOGICAL DISCUSSION

Dr. Guin:

As Dr. Ware predicted this patient had a thymoma, but the type was classified as benign rather than malignant. The operation was performed in March 1953, and follow-up information of this date (June 11, 1956), reveals the child is in excellent health. This tumor weighed 42.5 gm. and measured 8.5 x 7.5 cm. It was encapsulated and gave evidence of local hemorrhage.

It is perfectly true that histological study does not always answer the question as to whether a tumor is benign. The presence of hyperplasia is used as a criterion for the diagnosis of a thymoma. Histological appearance rather than gland weight alone is the important factor in evaluating hyperplasia.

The cell types normally present in the thymus gland include the lymphocytes (thymocytes), spindle epithelial cells, reticulum cells, and Hassall's corpuscles. Attempts to classify tumors of the thymus gland according to cell types have not been of practical value.

On gross examination the thymoma is likely to be a well encapsulated tumor. The weights are usually heavier if there is an associated myasthenia gravis.

In the event that the tumor is malignant, the gross findings are more likely to reveal local spread than distant metastases.

Microscopically, the lobular arrangement is usually preserved but a hyperplasia is noted which obscures the landmarks of cortex and medulla. The lymphocytes do not vary in size, but spindle shaped epithelial cells may be considerably enlarged. Squamous carcinoma of the thymus gland also occurs.

In any discussion of thymic tumors the question of myasthenia gravis arises. Even today, the value of thymectomy as a means of alleviating the symptoms of myasthenia gravis is not completely understood. At the Massachusetts General Hospital little benefit was noted in those patients suffering with myasthenia gravis who underwent thymectomy. This group included patients with thymomas and were mostly men with non-neoplasic thymus glands. However, the operation was considered to be of help in women below 30 years of age.

In a few cases of Cushing's syndrome, thymomas, both benign and malignant, have been reported.

The patient under discussion today is of interest not only because it is our first case of a thymoma, but because of the startling fact that this patient has a younger brother who was explored a year ago, and was also found to have a benign thymoma.

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*From an exhibit by Sydney H. Kane, M.D., at the American Medical Association meeting, Atlantic City, N. J., June 6-10, 1955.

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